

**Application No.:** 10/587,987  
**Filing Date:** December 2, 2008

## AMENDMENTS TO THE SPECIFICATION

Please insert the following new header and new paragraph after paragraph [0001]:

### Reference to Sequence Listing

The present application includes a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled MSCI003NP.TXT, created January 19, 2010, which is 23.9KB in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

Please replace original paragraph [0015] with the following re-written paragraph:

**[0015]** An additional embodiment provides for a complex peptide mixture, comprising a plurality of peptides having a length within the range of 8 to 20 amino acids, wherein said mixture comprises peptides having a degree of diversity at defined positions in the peptide chain, and wherein at least in a majority of the mixture, the identity of 9 contiguous amino acids in the peptides are defined by the formulas FW-EF-EK-AEK-AKY-ANY-ANY-AINV-ASV-Y (SEQ ID NO: 1) or EFWY-EFIVWY-EFKQ-AEKQ-AKQY-ANQY-AGNSY-AGINSV-AIQSV-IKRSVY (SEQ ID NO: 2). In some embodiments, position P1 of the 9 contiguous amino acid residues is the N-terminal peptide. Preferably, the N-terminal amino acid is acetylated. Advantageously, a majority of the peptides in the mixture have, in at least one position, the same amino acid. More advantageously, substantially all of the peptides in the mixture have, in at least one position, the same amino acid.

Please replace original paragraph [0031] with the following re-written paragraph:

**[0031]** Limiting the complexity of GA would allow an examination of individual properties of GA and their contribution to GA's immunomodulatory effects. Investigators made efforts to limit the complexity of GA by resorting to smaller molecules and/or improving efficacy by designing copolymers based on residues found in specific immunodominant T cell epitopes interacting with disease-associated MHC molecules. Based on interactions of MBP (85-99) with the HLA-DR molecule HLA-DRB1\*1501, novel random four-amino acid copolymers of 14, 35 or 50 a.a. in length were created with the introduction of F (phenylalanine) in place of glutamic acid (E) (Fridkis-Hareli et al., 2002). Both poly-FAK and poly-FEAK were more effective than

**Application No.:** 10/587,987  
**Filing Date:** December 2, 2008

GA in the inhibition of MBP(85-99)-specific HLA-DR2-restricted TCC activation. Poly-FAK and -FEAK also suppressed EAE in the SJL mouse strain more efficiently than GA. Another study synthesized peptides based on the motifs recently described for binding of MBP(85-99) and of GA to the groove of HLA-DR2 molecules, i.e. E at P2, K at P1, Y and A at P1, and A at P2-P11. Certain 15-mer peptides did indeed inhibit binding of MBP (85-99) to HLA-DR2 molecules more effectively than GA. Another report described ordered peptides of repetitive 4 amino acid (aa) sequences designed to bind critical MHC pockets and to interfere with T cell activation, based on MHC-TCR binding motifs for HLA-DR2 and MBP<sub>85-99</sub> (Ruiz et al., 2001). One such sequence, EYYKEYYKEYYK (SEQ ID NO: 3) was found to ameliorate EAE in Lewis rats. However, while it appears that synthetic copolymers tailored according to binding motifs of immunodominant epitopes and binding pockets of DR molecules can illuminate aspects of peptide interactions with MHC and TCR, use of single APLs has proven problematic in human clinical trials for MS treatment, as noted above (Bielekova et al., 2000; Kappos et al., 2000).

Please replace original paragraph [0048] with the following re-written paragraph:

[0048] Complex mixtures (CM) (Table 1, below) and myelin peptides were synthesized as first presented elsewhere by the simultaneous multiple peptide synthesis method, methyl-benzhydrylamine polystyrene resin, and t-Boc-protected L-amino acids (Houghten, R. *PNAS* **82**:5131-5135, and Houghten, R., et al. *Journal of Med Chem.* **42**:3743-3778, 1999, both of which are hereby incorporated by reference in their entireties). Myelin peptide pools: Proteolipid protein (PLP) peptides: PLP<sub>89-106</sub>-GFYTTGAVRQIFGDYKTT (SEQ ID NO: 4), PLP<sub>139-154</sub>-HCLGKWLGHPDKFVGI (SEQ ID NO: 5), PLP<sub>178-197</sub>-NTWTTTCQSIAFPSKTSASIG (SEQ ID NO: 6), PLP<sub>190-209</sub>-SKTSASIGSLCADARMYGV (SEQ ID NO: 7). Myelin basic protein (MBP) peptides: MBP<sub>13-32</sub>-KYLATASTMDHARHGFLPRH (SEQ ID NO: 8), MBP<sub>83-99</sub>-ENPVVHFFKNIVTPRTP (SEQ ID NO: 9), MBP<sub>111-129</sub>-LSRFWSWGAEGQRPGFGYGG (SEQ ID NO: 10), MBP<sub>131-155</sub>-ASDYKSAHKGLGVDAQGTLISKIFK (SEQ ID NO: 11), MBP<sub>146-170</sub>-AQGTLISKIFKLGGGRDSRGSP-MARR (SEQ ID NO: 12). Myelin oligodendrocyte glycoprotein (MOG) peptides: MOG<sub>1-20</sub>-CQFRVIGPRHPIRALVGDEV (SEQ ID NO: 13), MOG<sub>11-30</sub>-PIRALVGDEVELPCRISPGK (SEQ ID NO: 14), MOG<sub>21-40</sub>-

**Application No.:** 10/587,987  
**Filing Date:** December 2, 2008

ELPCRISPGKNATGMEVGWY      (SEQ      ID      NO:      15),      MOG<sub>35-55-</sub>  
MEVGWYRPPFSRVVHLYRNGK      (SEQ      ID      NO:      16).      2',3'-Cyclic nucleotide  
3'phosphodiesterase (CNPase) and myelin oligodendrocytic basic protein (MOBP) peptides:  
CNPase<sub>343-373</sub>-EVGELSRGKL YSLGNRGRWMLTLAKNMEVRAI (SEQ ID NO: 17), CNPase<sub>356-</sub>  
388-GNGRWMLTLAKNMEVRAIFTGYYGKGKPVPTQG (SEQ ID NO: 18), MOBP<sub>21-39-</sub>  
FSIHCCPPFTFNNSKKEIV (SEQ ID NO: 19) and MOBP<sub>31-49</sub>-FLNSKKEIVDRKYSICKSG  
(SEQ ID NO: 20). Peptides were characterized using an electrospray mass spectrophotometer  
interfaced with a liquid chromatography system. Glatiramer acetate (GA)/Copolymer-  
1/Copaxone was purchased from Teva Pharmaceuticals, (Teva Marion Partners, Kansas City,  
MO). PLP<sub>139-151</sub> peptide (sequence HSLGKWLGH<sup>P</sup>DKF (SEQ ID NO: 21)) was synthesized by  
Stanford Pan Facility (Palo Alto, CA). Human MBP was prepared as previously described  
(Deibler et al., 1972).

Please replace original Table 1 with the following re-written table:

Table 1. Nomenclature and Composition of Complex Mixtures (CM)

	<b>P1</b>	<b>P2</b>	<b>P3</b>	<b>P4</b>	<b>P5</b>	<b>P6</b>	<b>P7</b>	<b>P8</b>	<b>P9</b>	<b>P10</b>
<b>10 mers</b>	AEKY <sup>10</sup>	AEKY	AEKY <u>(SEQ ID NO: 22)</u>							
AEKY <sup>10</sup>	Ac-	AEKY	AEKY <u>(SEQ ID NO: 22)</u>							
AEKY <sup>GA</sup> *	AEKY <sup>GA</sup> *	AEKY	AEKY <u>(SEQ ID NO: 22)</u>							
AEKY <sup>GA</sup> *	Ac-	AEKY	AEKY <u>(SEQ ID NO: 22)</u>							
<b>12 mers</b>	AEKY <sup>12</sup>	AEKY	AEKY... <u>(SEQ ID NO: 23)</u>							
AEKY <sup>12</sup>	Ac-	AEKY	AEKY... <u>(SEQ ID NO: 23)</u>							
<b>15 mers</b>	AEKY <sup>15</sup>	AEKY	AEKY... <u>(SEQ ID NO: 24)</u>							
AEKY <sup>15</sup>	Ac-	AEKY	AEKY... <u>(SEQ ID NO: 24)</u>							
<b>20 mers</b>	AEKY <sup>20</sup>	AEKY	AEKY... <u>(SEQ ID NO: 25)</u>							
AEKY <sup>20</sup>	Ac-	AEKY	AEKY... <u>(SEQ ID NO: 25)</u>							
<b>DR2a bias</b>	AEKY <sup>10-DR2a</sup>	FLMY	AEKY	IMQV	AEKY	AEKY	AEKY	AEKY	KR	AEKY <u>(SEQ ID NO: 26)</u>
AEKY <sup>10-DR2a</sup>	Ac-	FLMY	AEKY	IMQV	AEKY	AEKY	AEKY	AEKY	KR	AEKY <u>(SEQ ID NO: 26)</u>
<b>DR2b bias</b>	AEKY <sup>10-DR2b</sup>	ILV	AEKY	IMQV	AEKY	AEKY	FILMV	AEKY	AEKY	AEKY <u>(SEQ ID NO: 27)</u>
AEKY <sup>10-DR2b</sup>	Ac-	ILV	AEKY	IMQV	AEKY	AEKY	FILMV	AEKY	AEKY	AEKY <u>(SEQ ID NO: 27)</u>
<b>GA clone driven</b>	GA TCC-1 <sup>10</sup>	Ac-	FW	EF	AEK	AKY	ANY	AINV	ASV	Y <u>(SEQ ID NO: 28)</u>
GA TCC-2 <sup>10</sup>	Ac-	EFWY	EFWY	EFKQ	AEKQ	AKQY	ANQY	AGNSY	AIQSV	IKRSVY <u>(SEQ ID NO: 29)</u>
<b>IAs bias</b>	19a.a. <sup>10-las</sup>	Ac-	X	X	X	X	ILV	ILV	X	P1 <u>(SEQ ID NO: 30)</u>
AEKY <sup>10-las</sup>	Ac-	AEKY	AEKY	AEKY	AEKY	AEKY	KHRV	X	AEKY	P1 <u>(SEQ ID NO: 31)</u>

Application No.: 10/587,987  
Filing Date: December 2, 2008

	AEKY <sup>10</sup> -As-mis	Ac-	PI	HRK	ILV	KHRV	AEKY	AEKY	AEKY	AEKY	(SEQ ID NO: 32)
Random amino acids											
19 a.a. <sup>10</sup>	X	X	X	X	X	X	X	X	X	X	(SEQ ID NO: 33)

For each CM, the amino acid which could be present at each position in the random peptide mixture is listed in the chart. As shown above, the 10mer AEKY10 could have A, E, K, or Y in each of the 10 peptide positions. Alternatively, DR2a-biased CM AEKY10-DR2a could contain any of the FLMY anchor residues in P1, but no other aa. \* GA indicates that the aa A,E,K and Y were present at ratios similar to that used in GA prior to the synthesis (6:2.5:1), whereas other mixtures contain the listed aa at each position at equimolar ratios. X represents any of the 19 non-cysteine standard amino acids.

Please replace the original table after paragraph [0063] with the following re-written table:

		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	<u>SEQ ID NO.</u>
AEKY <sup>10-IAs</sup>	Ac-	AEKY	AEKY	AEKY	AEKY	KHRV	AEKY	ILV	HRK	AEKY	PI	<u>31</u>
19a.a. <sup>10-IAs</sup>	Ac-	X	X	X	X	KHRV	X	ILV	HRK	X	PI	<u>30</u>

X = equimolar amount of all 20 L amino acids excluding Cysteine

Please replace original Table 4 with the following re-written table:

Table 4. Formulas for optimization of complex mixtures experiment

AEKY <sup>10-IAs</sup>		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	<u>SEQ ID NO.</u>
Original	Ac-	AEKY	AEKY	AEKY	AEKY	KHRV	AEKY	ILV	HRK	AEKY	PI	<u>31</u>
Sample - 1	Ac-	AEKY	AEKY	AEKY	AEKY	A	AEKY	ILV	HRK	AEKY	PI	<u>34</u>
Sample - 2	Ac-	AEKY	AEKY	AEKY	AEKY	C	AEKY	ILV	HRK	AEKY	PI	<u>35</u>
Sample - 3	Ac-	AEKY	AEKY	AEKY	AEKY	D	AEKY	ILV	HRK	AEKY	PI	<u>36</u>
Sample - 4	Ac-	AEKY	AEKY	AEKY	AEKY	E	AEKY	ILV	HRK	AEKY	PI	<u>37</u>
Sample - 5	Ac-	AEKY	AEKY	AEKY	AEKY	F	AEKY	ILV	HRK	AEKY	PI	<u>38</u>
Sample - 6	Ac-	AEKY	AEKY	AEKY	AEKY	G	AEKY	ILV	HRK	AEKY	PI	<u>39</u>
Sample - 7	Ac-	AEKY	AEKY	AEKY	AEKY	H	AEKY	ILV	HRK	AEKY	PI	<u>40</u>
Sample - 8	Ac-	AEKY	AEKY	AEKY	AEKY	I	AEKY	ILV	HRK	AEKY	PI	<u>41</u>
Sample - 9	Ac-	AEKY	AEKY	AEKY	AEKY	K	AEKY	ILV	HRK	AEKY	PI	<u>42</u>
Sample - 10	Ac-	AEKY	AEKY	AEKY	AEKY	L	AEKY	ILV	HRK	AEKY	PI	<u>43</u>
Sample - 11	Ac-	AEKY	AEKY	AEKY	AEKY	M	AEKY	ILV	HRK	AEKY	PI	<u>44</u>
Sample - 12	Ac-	AEKY	AEKY	AEKY	AEKY	N	AEKY	ILV	HRK	AEKY	PI	<u>45</u>
Sample - 13	Ac-	AEKY	AEKY	AEKY	AEKY	P	AEKY	ILV	HRK	AEKY	PI	<u>46</u>
Sample - 14	Ac-	AEKY	AEKY	AEKY	AEKY	Q	AEKY	ILV	HRK	AEKY	PI	<u>47</u>
Sample - 15	Ac-	AEKY	AEKY	AEKY	AEKY	R	AEKY	ILV	HRK	AEKY	PI	<u>48</u>
Sample - 16	Ac-	AEKY	AEKY	AEKY	AEKY	S	AEKY	ILV	HRK	AEKY	PI	<u>49</u>
Sample - 17	Ac-	AEKY	AEKY	AEKY	AEKY	T	AEKY	ILV	HRK	AEKY	PI	<u>50</u>
Sample - 18	Ac-	AEKY	AEKY	AEKY	AEKY	V	AEKY	ILV	HRK	AEKY	PI	<u>51</u>
Sample - 19	Ac-	AEKY	AEKY	AEKY	AEKY	W	AEKY	ILV	HRK	AEKY	PI	<u>52</u>
Sample - 20	Ac-	AEKY	AEKY	AEKY	AEKY	Y	AEKY	ILV	HRK	AEKY	PI	<u>53</u>
Sample - 21	Ac-	A	AEKY	AEKY	AEKY	KHRV	AEKY	ILV	HRK	AEKY	PI	<u>54</u>
Sample - 22	Ac-	C	AEKY	AEKY	AEKY	KHRV	AEKY	ILV	HRK	AEKY	PI	<u>55</u>
•••												
Sample - 40	Ac-	Y	AEKY	AEKY	AEKY	KHRV	AEKY	ILV	HRK	AEKY	PI	<u>56</u>